Clinical trial results:
Phase IIa, Randomised, Controlled, Open-Label Trial of Rosuvastatin for the Prevention of Aminoglycoside-Induced Kidney Toxicity in Children with Cystic Fibrosis

Summary

EudraCT number	2014-002387-32
Trial protocol	GB
Global end of trial date	17 March 2017

Results information

Result version number	v1 (current)
This version publication date	01 November 2018
First version publication date	01 November 2018
Summary attachment (see zip file)	Final Analysis Report v2.0 (PROteKT Final Analysis Report v2.0 11-10-18.pdf)

Trial information

Trial identification

Sponsor protocol code	UoL001019

Additional study identifiers

ISRCTN number	ISRCTN26104255
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC number: 14/NW/1067, IRAS project ID: 137736

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
Sponsor organisation address	2nd Floor Block D Waterhouse Building, 3 Brownlow Street, Liverpool, United Kingdom, L69 3GL
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 February 2017
Global end of trial reached?	Yes
Global end of trial date	17 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does rosuvastatin protect against kidney damage caused by aminoglycoside antibiotics?

This will be assessed by comparing the difference in the change in the urine biomarker KIM-1 from baseline to 'highest concentration' during exposure to tobramycin between the rosuvastatin treated arm and control arm.

Protection of trial subjects:

The patient was instructed in the correct use of the medications dispensed. Further guidance was available throughout the remainder of the trial where necessary.

Study visits and study assessments were set around routine clinical care to minimise the inconvenience for patients and families.

Background therapy:

This study included only children with CF treated with the aminoglycoside antibiotic tobramycin given intravenously. IV tobramycin is usually given once daily, but can also be given three times per day. Participants could receive tobramycin at either frequency (as decided by the local CF team on clinical grounds), and was specified in the study CRFs with the time and amount of each dose.

Evidence for comparator:

For full details refer to the protocol. In summary, given the mechanism of action of aminoglycosides in causing nephrotoxicity, statins are a possible intervention. Statins are drugs widely used in cardiovascular disease in adults, with proven efficacy and safety. Statins are also used in children having been licensed principally for the treatment of hyperlipidaemia.

Actual start date of recruitment	29 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	22
Adolescents (12-17 years)	28
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first site was opened on 14-May-2015 and the first participant was randomised on 29-Jun-2015. The last participant was randomised on 23-Jan-2017.

Pre-assignment

Screening details:

258 were assessed for eligibility, of which 126 (49%) were eligible and 50 (40%) were randomised.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Non intervention arm

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Rosuvastatin

Arm description:

Oral rosuvastatin 10 milligram (mg) dose, once daily, for the duration of a treatment course of IV tobramycin (usually 14 days)

Arm type	Experimental
Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	Brand name: Crestor®
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral rosuvastatin 10 milligram (mg) dose, once daily, for the duration of a treatment course of IV tobramycin (usually 14 days)

Number of subjects in period 1	Control	Rosuvastatin
Started	27	23
Completed	26	23
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Non intervention arm	
Reporting group title	Rosuvastatin
Reporting group description:	
Oral rosuvastatin 10 milligram (mg) dose, once daily, for the duration of a treatment course of IV tobramycin (usually 14 days)	

Reporting group values	Control	Rosuvastatin	Total
Number of subjects	27	23	50
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	8	14	22
Adolescents (12-17 years)	19	9	28
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	13.30	12.09	
standard deviation	± 2.65	± 2.74	-
Gender categorical			
Units: Subjects			
Female	19	13	32
Male	8	10	18
Ethnic origin			
Units: Subjects			
White	27	21	48
Other White	0	1	1
Mixed: White and Black African	0	1	1
Height			
Units: cm			
arithmetic mean	151.93	148.43	
standard deviation	± 16.07	± 15.79	-
Weight			
Units: kilogram(s)			
arithmetic mean	44.67	40.63	
standard deviation	± 15.58	± 14.98	-
Serum creatinine			
Units: µmol/L			
arithmetic mean	45.30	43.57	

standard deviation	± 10.56	± 11.52	-
Estimated Glomerular Filtration Rate			
Units: mL/min/1.73m^2			
arithmetic mean	139.90	142.21	
standard deviation	± 29.69	± 27.02	-
Aspartate transaminase			
Units: iu/L			
arithmetic mean	28.77	33.41	
standard deviation	± 11.09	± 17.69	-
Alanine transaminase			
Units: iu/L			
arithmetic mean	25.48	27.77	
standard deviation	± 16.53	± 17.09	-
HDL cholesterol			
Units: mmol/L			
arithmetic mean	1.06	1.09	
standard deviation	± 0.32	± 0.40	-
LDL cholesterol			
Units: mmol/L			
arithmetic mean	1.47	1.25	
standard deviation	± 0.54	± 0.55	-
Total cholesterol			
Units: mmol/L			
arithmetic mean	2.80	2.75	
standard deviation	± 0.67	± 0.66	-
Triglycerides			
Units: mmol/L			
arithmetic mean	1.17	1.00	
standard deviation	± 0.77	± 0.53	-
Creatine kinase			
Units: iu/L			
arithmetic mean	67.15	83.83	
standard deviation	± 33.13	± 55.31	-
C Reactive Protein			
Units: mg/L			
arithmetic mean	10.46	7.48	
standard deviation	± 14.29	± 8.41	-
FEV in 1 second			
Units: litre(s)			
arithmetic mean	2.10	1.86	
standard deviation	± 1.30	± 0.91	-
FEV in 1 second (% predicted)			
Units: percent			
arithmetic mean	74.05	73.98	
standard deviation	± 17.57	± 19.59	-
KIM-1 (normalised to urinary creatinine)			
Units: ng/mgCr			
arithmetic mean	1.94	0.67	
standard deviation	± 2.45	± 0.45	-
NGAL (normalised to urinary creatinine)			
Units: ng/mgCr			
arithmetic mean	61.08	22.46	

standard deviation	± 89.55	± 22.99	-

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Non intervention arm	
Reporting group title	Rosuvastatin
Reporting group description:	
Oral rosuvastatin 10 milligram (mg) dose, once daily, for the duration of a treatment course of IV tobramycin (usually 14 days)	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants with valid (non-missing) data were analysed according to the groups to which they were randomised.	

Primary: Primary Outcome

End point title	Primary Outcome
End point description:	
The primary outcome measure is the difference in mean fold-change in urinary KIM-1 from baseline to peak concentration during exposure to tobramycin between the rosuvastatin treated group and control group.	
End point type	Primary
End point timeframe:	
Duration of exposure to tobramycin treatment.	

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[1]	20[2]		
Units: N/A - Average mean fold-change				
number (not applicable)	1.85	2.00		

Notes:

[1] - 3 baseline samples were invalid.

[2] - 1 baseline sample was invalid; 2 withdrew after baseline and had missing baseline samples.

Statistical analyses

Statistical analysis title	Primary efficacy assessment
Statistical analysis description:	
An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to peak KIM-1 normalised to urinary creatinine between the treatment groups, controlling for the baseline normalised KIM-1. The model estimates were exponentiated to be interpretable on the normal scale.	
Comparison groups	Control v Rosuvastatin

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.35

Secondary: Change in serum concentration of creatinine during tobramycin exposure

End point title	Change in serum concentration of creatinine during tobramycin exposure

End point description:

A random intercept model including an interaction term between time and treatment was used to compare serum concentration of creatinine during tobramycin exposure between the treatment groups at each of the specified time points.

End point type	Secondary

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	23		
Units: mmol/L				
number (not applicable)				
Baseline	44.81	43.87		
T+1	54.55	46.67		
T+8	48.23	46.09		
T+13/last treatment	42.84	42.00		
Overall	47.61	44.66		

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

Difference in serum concentration of creatinine during tobramycin exposure between the rosuvastatin and control group: Random intercept model results

Comparison groups	Control v Rosuvastatin

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.61
upper limit	3.71

Notes:

[3] - T+1: P=0.07
T+8: P=0.62
T+13/last treatment: P=0.88

Secondary: Change in eGFR during tobramycin exposure

End point title	Change in eGFR during tobramycin exposure

End point description:

A random intercept model including an interaction term between time and treatment was used to compare eGFR during tobramycin exposure between the treatment groups at each of the specified time points.

End point type	Secondary

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	23		
Units: mmol/L				
number (not applicable)				
Baseline	139.90	142.21		
T+8	144.84	137.46		
T+13/last treatment	141.30	142.09		
Overall	142.01	140.59		

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

Difference in eGFR during tobramycin exposure between the rosuvastatin and control group: Random intercept model results

Comparison groups	Control v Rosuvastatin

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.64
upper limit	13.78

Notes:

[4] - T+8: P=0.43
T+13/last treatment: P=0.95

Secondary: Difference in other urinary and plasma biomarkers of renal injury during tobramycin exposure

End point title	Difference in other urinary and plasma biomarkers of renal injury during tobramycin exposure

End point description:

A random intercept model including an interaction term between time and treatment was used to compare NGAL during tobramycin exposure between the treatment groups at each of the specified time points.

End point type	Secondary

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	21[5]		
Units: ng/mgCr				
number (not applicable)				
Baseline	58.78	21.94		
T+1	105.92	79.03		
T+2	83.18	31.33		
T+3	66.82	33.60		
T+4	100.14	38.47		
T+5	86.73	33.88		
T+6	97.70	37.15		
T+7	109.27	40.46		
T+8	92.43	39.02		
T+9	111.59	42.35		
T+10	110.65	87.44		
T+11	152.56	81.02		
T+12	100.16	54.86		
T+13	88.28	50.59		
T+14	162.05	34.51		
Overall	101.75	47.04		

Notes:

[5] - 2 participants withdrew after baseline and had missing baseline samples.

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

A random intercept model including an interaction term between time and treatment was used to compare NGAL during tobramycin exposure between the treatment groups at each of the specified time points.

Comparison groups	Rosuvastatin v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-54.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-102.25
upper limit	-7.16

Notes:

[6] - T+1: p=0.47
T+2: p=0.18
T+3: p=0.39
T+4: p=0.12
T+5: p=0.17
T+6: p=0.12
T+7: p=0.09
T+8: p=0.17
T+9: p=0.09
T+10: p=0.57
T+11: p=0.08
T+12: p=0.28
T+13: p=0.41
T+14: p=0.19

Secondary: Difference in tobramycin concentrations between rosuvastatin treated group and the control group to identify any pharmacokinetic interaction between rosuvastatin and the tobramycin

End point title	Difference in tobramycin concentrations between rosuvastatin treated group and the control group to identify any pharmacokinetic interaction between rosuvastatin and the tobramycin

End point description:

The non-linear mixed model did not converge and thus the analysis outlined in the Statistical Analysis Plan was not possible.

End point type	Secondary

End point timeframe:

A blood sample to measure tobramycin concentrations was taken on T+1, T+8 and T+13 days (or final day of tobramycin treatment if earlier than T+13), final day of tobramycin (if later than T+13) during tobramycin exposure and at any unscheduled visits.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	21[7]		
Units: N/A				
number (not applicable)	27	21		

Notes:

[7] - 2 participants withdrew after baseline and had missing baseline samples.

Statistical analyses

No statistical analyses for this end point

Secondary: Difference in Forced Expiratory Volume in 1 second (FEV1)

End point title	Difference in Forced Expiratory Volume in 1 second (FEV1)

End point description:

A random intercept model including an interaction term between time and treatment was used to compare FEV1 during tobramycin exposure between the treatment groups at each of the specified time points.

End point type	Secondary

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	21[8]		
Units: Litres				
number (not applicable)				
Baseline	2.10	1.86		
T+8	1.88	2.00		
T+13/last treatment	1.84	1.94		
Overall	1.94	1.93		

Notes:

[8] - 2 participants withdrew after baseline and had missing baseline samples.

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

A random intercept model including an interaction term between time and treatment was used to compare FEV1 during tobramycin exposure between the treatment groups at each of the specified time points.

Comparison groups	Control v Rosuvastatin

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.49

Notes:

[9] - T+8: p=0.67
T+13/last treatment: p=0.77

Secondary: Difference in C Reactive Protein (CRP)

End point title	Difference in C Reactive Protein (CRP)

End point description:

A random intercept model including an interaction term between time and treatment was used to compare CRPduring tobramycin exposure between the treatment groups at each of the specified time points.

End point type	Secondary

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	23		
Units: mg/L				
number (not applicable)				
Baseline	10.46	7.48		
T+1	15.63	7.42		
T+8	4.96	4.75		
T+13/last treatment	4.95	3.93		
Overall	9.00	5.89		

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

A random intercept model including an interaction term between time and treatment was used to compare CRP during tobramycin exposure between the treatment groups at each of the specified time points.

Comparison groups	Control v Rosuvastatin

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.68
upper limit	1.46

Secondary: Relationship between plasma rosuvastatin concentrations achieved in children randomised to the intervention group and change in urinary KIM-1

End point title	Relationship between plasma rosuvastatin concentrations achieved in children randomised to the intervention group and change in urinary KIM-1[10]

End point description:

The mean (SD) rosuvastatin levels were compared against the mean (SD) KIM-1 normalised to urinary creatinine at each time point. See Final Analysis Report upload for full results.

End point type	Secondary

End point timeframe:

Duration of exposure to tobramycin treatment.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was only applicable to participants in the rosuvastatin arm

End point values	Rosuvastatin			
Subject group type	Reporting group			
Number of subjects analysed	16[11]			
Units: Rosuvastatin level				
arithmetic mean (standard deviation)				
T0	0.10 (± 0.36)			
T+1	3.25 (± 4.88)			
T+8	1.56 (± 1.13)			
T+13	1.22 (± 1.37)			
4 weeks following treatment cessation	0.33 (± 1.09)			

Notes:

[11] - Only subjects with a valid rosuvastatin sample were included.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Primary Outcome - Sensitivity Analysis 1

End point title	Primary Outcome - Sensitivity Analysis 1

End point description:

Sensitivity analysis 1 compared the difference in normalised KIM-1 from baseline to final day of treatment. For participants with a missing sample on day of last treatment, the result from the latest sample taken before the end of treatment was used. An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to last day of treatment between the treatment groups, controlling for baseline normalised KIM-1.The model estimates were exponentiated to be interpretable on the normal scale.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[12]	20[13]		
Units: N/A - Average mean fold-change				
number (not applicable)	1.36	1.48		

Notes:

[12] - 3 baseline samples were invalid.

[13] - 1 baseline sample was invalid; 2 withdrew after baseline and had missing baseline samples.

Statistical analyses

Statistical analysis title	Primary Outcome - Sensitivity Analysis 1

Statistical analysis description:

An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to last day of treatment between the treatment groups, controlling for baseline normalised KIM-1. The model estimates were exponentiated to be interpretable on the normal scale.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.39

Other pre-specified: Primary Outcome – Sensitivity Analysis 2

End point title	Primary Outcome – Sensitivity Analysis 2

End point description:

Sensitivity analysis 2 was a repeat of the analysis of the primary outcome, excluding those who returned less than 50% of urine samples. Two participants, each with 57% of samples missing, one in the control group and one in the rosuvastatin group, were excluded from this analysis.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[14]	19[15]		
Units: N/A - Average mean fold-change				
number (not applicable)	1.89	2.03		

Notes:

[14] - 3 baseline samples were invalid; 1 had >50% of samples missing.

[15] - 1 baseline sample was invalid; 2 withdrew at baseline; one had >50% of samples missing.

Statistical analyses

Statistical analysis title	Primary Outcome – Sensitivity Analysis 2

Statistical analysis description:

Sensitivity analysis 2 was a repeat of the analysis of the primary outcome, excluding those who returned less than 50% of urine samples. Two participants, each with 57% of samples missing, one in the control group and one in the rosuvastatin group, were excluded from this analysis.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.34

Other pre-specified: Primary Outcome - Sensitivity Analysis 3

End point title	Primary Outcome - Sensitivity Analysis 3

End point description:

Sensitivity analysis 3 was a repeat of the analysis of the primary outcome, including participants who had a missing baseline sample by imputing their baseline result as the mean normalised KIM-1 value over all observed baseline KIM-1 values.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	21[16]		
Units: N/A - Average mean fold-change				
number (not applicable)	2.10	1.35		

Notes:

[16] - 2 participants withdrew after baseline and had missing baseline samples.

Statistical analyses

Statistical analysis title	Primary Outcome – Sensitivity Analysis 3

Statistical analysis description:

An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to peak KIM-1 normalised to urinary creatinine between the treatment groups, controlling for the baseline normalised KIM-1. The model estimates were exponentiated to be interpretable on the normal scale.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.1

Other pre-specified: Primary Outcome – Sensitivity Analysis 4

End point title	Primary Outcome – Sensitivity Analysis 4

End point description:

Sensitivity analysis 4 was a repeat of the analysis of the primary outcome, accounting for a random effect for centre using a random intercept model.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[17]	20[18]		
Units: N/A - Average mean fold-change				
number (not applicable)	1.82	1.99		

Notes:

[17] - 3 baseline samples were invalid.

[18] - 1 baseline sample was invalid; 2 withdrew at baseline and had missing samples.

Statistical analyses

Statistical analysis title	Primary Outcome - Sensitivity Analysis 4

Statistical analysis description:

An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to peak concentration between the treatment groups, controlling for baseline normalised KIM-1, including centre as a random effect. The model estimates were exponentiated to be interpretable on the normal scale.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.34

Other pre-specified: Primary Outcome – Sensitivity Analysis 5

End point title	Primary Outcome – Sensitivity Analysis 5

End point description:

Sensitivity analysis 5 was a repeat of the analysis of the primary outcome, excluding any normalised KIM-1 results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[19]	20[20]		
Units: N/A - Average mean fold-change				
number (not applicable)	1.89	1.92		

Notes:

[19] - Analysis excluded statistical outliers

[20] - Analysis excluded statistical outliers

Statistical analyses

Statistical analysis title	Primary Outcome – Sensitivity Analysis 5

Statistical analysis description:

An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to last day of treatment between the treatment groups, controlling for baseline normalised KIM-1. The model estimates were exponentiated to be interpretable on the normal scale.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.24

Other pre-specified: Primary Outcome – Additional Analysis: Area under the curve (AUC)

End point title	Primary Outcome – Additional Analysis: Area under the curve (AUC)

End point description:

The area under the curve (AUC) of normalised KIM-1 was compared between the two treatment groups using a T-test.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	21[21]		
Units: ng/mgCr				
arithmetic mean (standard deviation)	23.05 (± 33.02)	10.65 (± 6.11)		

Notes:

[21] - 2 participants withdrew after baseline and had missing samples.

Statistical analyses

Statistical analysis title	Primary Outcome – Additional Analysis: AUC

Statistical analysis description:

The area under the curve (AUC) of normalised KIM-1 was compared between the two treatment groups using a T-test.

Comparison groups	Control v Rosuvastatin

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	12.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	25.7

Other pre-specified: Change in serum concentration of creatinine during tobramycin exposure - Sensitivity Analysis

End point title	Change in serum concentration of creatinine during tobramycin exposure - Sensitivity Analysis

End point description:

A random intercept model including an interaction term between time and treatment was used to compare serum concentration of creatinine during tobramycin exposure between the treatment groups at each of the specified time points.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	23		
Units: mmol/L				
number (not applicable)				
Baseline	44.81	43.87		
T+1	50.15	44.98		
T+8	45.21	46.04		
T+13/last treatment	45.00	41.83		
Overall	46.29	44.18		

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

A random intercept model including an interaction term between time and treatment was used to compare serum concentration of creatinine during tobramycin exposure between the treatment groups at each of the specified time points. A sensitivity analysis was undertaken excluding any serum creatinine results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

Comparison groups	Control v Rosuvastatin

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48 [22]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.12
upper limit	3.9

Notes:

[22] - T+1: P=0.13
T+8: P=0.80
T+13/last treatment: P=0.40

Other pre-specified: Change in eGFR during tobramycin exposure - Sensitivity Analysis

End point title	Change in eGFR during tobramycin exposure - Sensitivity Analysis

End point description:

A random intercept model including an interaction term between time and treatment was used to compare eGFR during tobramycin exposure between the treatment groups at each of the specified time points.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	22[23]		
Units: mmol/L				
number (not applicable)				
Baseline	139.90	139.03		
T+8	144.81	135.79		
T+13/last treatment	141.38	140.27		
Overall	142.03	138.37		

Notes:

[23] - Statistical outliers removed

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

A random intercept model including an interaction term between time and treatment was used to compare eGFR during tobramycin exposure between the treatment groups at each of the specified time points. A sensitivity analysis was undertaken excluding any serum creatinine results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

Comparison groups	Control v Rosuvastatin

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.36
upper limit	11.03

Other pre-specified: Difference in other urinary and plasma biomarkers of renal injury during tobramycin exposure - Sensitivity Analysis

End point title	Difference in other urinary and plasma biomarkers of renal injury during tobramycin exposure - Sensitivity Analysis

End point description:

A random intercept model including an interaction term between time and treatment was used to compare NGAL during tobramycin exposure between the treatment groups at each of the specified time points. A sensitivity analysis was undertaken excluding any NGAL results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[24]	21[25]		
Units: ng/mgCr				
number (not applicable)				
Baseline	41.26	21.94		
T+1	42.01	34.12		
T+2	38.42	31.33		
T+3	43.13	34.20		
T+4	41.34	39.89		
T+5	55.29	29.98		
T+6	41.24	32.93		
T+7	38.65	36.71		
T+8	49.65	27.79		
T+9	50.08	43.22		
T+10	48.64	31.64		
T+11	45.85	34.64		
T+12	40.24	26.02		
T+13	50.59	38.53		
T+14	41.29	27.14		

Overall	44.51	32.67		

Notes:

[24] - Statistical outliers were excluded

[25] - Statistical outliers were excluded

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

A random intercept model including an interaction term between time and treatment was used to compare NGAL during tobramycin exposure between the treatment groups at each of the specified time points. A sensitivity analysis was undertaken excluding any NGAL results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12 [26]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-11.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.96
upper limit	3.28

Notes:

[26] - T+1: p=0.46
T+2: p=0.50
T+3: p=0.40
T+4: p=0.90
T+5: p=0.02
T+6: p=0.45
T+7: p=0.86
T+8: p=0.05
T+9: p=0.54
T+10: p=0.15
T+11: p=0.32
T+12: p=0.23
T+13: p=0.33
T+14: p=0.61

Other pre-specified: Change from baseline to peak NGAL

End point title	Change from baseline to peak NGAL

End point description:

Comparison of the difference in mean fold-change in urinary KIM-1 from baseline to peak concentration during exposure to tobramycin between the rosuvastatin treated group and control group.

End point type	Other pre-specified

End point timeframe:

Duration of tobramycin exposure.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[27]	20[28]		
Units: N/A - Average mean fold-change				
number (not applicable)	8.90	4.99		

Notes:

[27] - 3 baseline samples were invalid.

[28] - 1 baseline sample was invalid; 2 withdrew after baseline and had missing samples.

Statistical analyses

Statistical analysis title	Change from baseline to peak NGAL

Statistical analysis description:

An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to peak NGAL normalised to urinary creatinine between the treatment groups, controlling for the baseline normalised NGAL. The model estimates were exponentiated to be interpretable on the normal scale.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.15

Other pre-specified: Change from baseline to peak NGAL - Sensitivity Analysis

End point title	Change from baseline to peak NGAL - Sensitivity Analysis

End point description:

Comparison of the difference in mean fold-change in urinary KIM-1 from baseline to peak concentration during exposure to tobramycin between the rosuvastatin treated group and control group removing statistical outliers.

End point type	Other pre-specified

End point timeframe:

Duration of tobramycin exposure.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[29]	20[30]		
Units: N/A - Mean fold-change				
number (not applicable)	3.32	3.26		

Notes:

[29] - 3 baseline samples were invalid.

[30] - 1 baseline sample was invalid; 2 withdrew after baseline and had missing samples.

Statistical analyses

Statistical analysis title	Change from baseline to peak NGAL

Statistical analysis description:

An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to peak NGAL between the treatment groups, controlling for the baseline normalised NGAL. The model estimates were exponentiated to be interpretable on the normal scale. This sensitivity analysis excluded any normalised NGAL results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.72

Other pre-specified: NGAL: Area Under the Curve

End point title	NGAL: Area Under the Curve

End point description:

The area under the curve (AUC) of normalised NGAL was compared between the two treatment groups using a T-test.

End point type	Other pre-specified

End point timeframe:

Duration of tobramycin exposure.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	21[31]		
Units: (ng/mgCr)^2				
arithmetic mean (standard deviation)	1139.4 (± 1106.1)	581.6 (± 630.8)		

Notes:

[31] - 2 participants withdrew at baseline

Statistical analyses

Statistical analysis title	NGAL: AUC

Statistical analysis description:

The area under the curve (AUC) of normalised NGAL was compared between the two treatment groups using a T-test.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	557.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.5
upper limit	1069.2

Other pre-specified: Difference in Forced Expiratory Volume in 1 second (FEV1) - Sensitivity Analysis

End point title	Difference in Forced Expiratory Volume in 1 second (FEV1) - Sensitivity Analysis

End point description:

A random intercept model including an interaction term between time and treatment was used to compare FEV1 during tobramycin exposure between the treatment groups at each of the specified time points excluding statistical outliers.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[32]	20[33]		
Units: Litres				
number (not applicable)				
Baseline	1.80	1.75		
T+8	1.85	1.87		
T+13/last treatment	1.87	1.89		
Overall	1.84	1.84		

Notes:

[32] - Statistical outliers were excluded

[33] - Statistical outliers were excluded

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

A random intercept model including an interaction term between time and treatment was used to compare FEV1 during tobramycin exposure between the treatment groups at each of the specified time points. A sensitivity analysis was undertaken excluding any FEV1 results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99 [34]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.42

Notes:

[34] - T+8: p=0.93
T+13/last treatment: p=0.93

Other pre-specified: Difference in C Reactive Protein (CRP) - Sensitivity Analysis

End point title	Difference in C Reactive Protein (CRP) - Sensitivity Analysis

End point description:

A random intercept model including an interaction term between time and treatment was used to compare CRP during tobramycin exposure between the treatment groups at each of the specified time points excluding statistical outliers.

End point type	Other pre-specified

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[35]	19[36]		
Units: mg/L				
number (not applicable)				
Baseline	4.98	4.21		
T+1	5.59	4.34		
T+8	4.48	3.97		
T+13/last treatment	3.65	3.94		
Overall	4.67	4.12		

Notes:

[35] - Statistical outliers were excluded.

[36] - Statistical outliers were excluded.

Statistical analyses

Statistical analysis title	Random intercept

Statistical analysis description:

A random intercept model including an interaction term between time and treatment was used to compare CRP during tobramycin exposure between the treatment groups at each of the specified time points. A sensitivity analysis was undertaken excluding any CRP results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [37]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.52
upper limit	0.41

Notes:

[37] - T+1: p=0.07
T+8: p=0.41
T+13/last treatment: p=0.69

Post-hoc: Primary outcome adjusted for age

End point title	Primary outcome adjusted for age

End point description:

The primary outcome analysis was repeated, controlling for age.

End point type	Post-hoc

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[38]	20[39]		
Units: N/A - Average mean fold-change				
number (not applicable)	1.88	1.95		

Notes:

[38] - 3 baseline samples were invalid.

[39] - 1 baseline sample was invalid; 2 withdrew after baseline and had missing samples.

Statistical analyses

Statistical analysis title	Primary Outcome adjusted for age: ANCOVA results

Statistical analysis description:

An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to peak KIM-1 normalised to urinary creatinine between the treatment groups, controlling for the baseline normalised KIM-1 and age. The model estimates were exponentiated to be interpretable on the normal scale.

Comparison groups	Control v Rosuvastatin

Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.75
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.29

Post-hoc: Primary Outcome: Area under the curve - Sensitivity Analysis

End point title	Primary Outcome: Area under the curve - Sensitivity Analysis

End point description:

End point type	Post-hoc

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[40]	21[41]		
Units: (ng/mgCr)^2				
arithmetic mean (standard deviation)	10.79 (± 6.66)	10.07 (± 5.31)		

Notes:

[40] - Statistical outliers were excluded.

[41] - Statistical outliers were excluded.

Statistical analyses

Statistical analysis title	KIM-1 AUC: Sensitivity analysis – T-test results

Statistical analysis description:

The area under the curve (AUC) of normalised KIM-1 was repeated, excluding any results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.69
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.92
upper limit	4.38

Post-hoc: NGAL: Area under the curve - Sensitivity Analysis

End point title	NGAL: Area under the curve - Sensitivity Analysis

End point description:

The area under the curve (AUC) of normalised NGAL was repeated, excluding any results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

End point type	Post-hoc

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	21[42]		
Units: (ng/mgCr)^2				
arithmetic mean (standard deviation)	511.0 (± 341.6)	416.6 (± 350.4)		

Notes:

[42] - 2 participants withdrew at baseline

Statistical analyses

Statistical analysis title	NGAL AUC: Sensitivity analysis – T-test results

Statistical analysis description:

The area under the curve (AUC) of normalised KIM-1 was repeated, excluding any results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.35
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	94.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-108.9
upper limit	297.9

Post-hoc: Difference in tobramycin concentrations between rosuvastatin treated group and the control group to identify any pharmacokinetic interaction between rosuvastatin and the tobramycin groups

End point title	Difference in tobramycin concentrations between rosuvastatin treated group and the control group to identify any pharmacokinetic interaction between rosuvastatin and the tobramycin groups

End point description:

A linear mixed model was fitted to the tobramycin concentration data using a random intercept and adjusting for time since last dose of tobramycin; an interaction between visit and treatment group was included.

End point type	Post-hoc

End point timeframe:

Duration of exposure to tobramycin treatment.

End point values	Control	Rosuvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[43]	20[44]		
Units: mg/L				
number (not applicable)				
T+1	0.34	0.40		
T+8	0.45	0.58		
T+13/last treatment	3.63	2.72		
Overall	1.24	1.47		

Notes:

[43] - Only subjects with a valid tobramycin concentration were included.

[44] - Only subjects with a valid tobramycin concentration were included.

Statistical analyses

Statistical analysis title	Random intercept model

Statistical analysis description:

A linear mixed model was fitted to the tobramycin concentration data using a random intercept and adjusting for time since last dose of tobramycin; an interaction between visit and treatment group was included.

Comparison groups	Control v Rosuvastatin
Number of subjects included in analysis	45
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.7 [45]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	1.02

Notes:

[45] - T+1: p=0.95
T+8: p=0.90
T+13/last treatment: p=0.41

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety events were recorded from the point that the participant provides informed consent and throughout the trial treatment period up until the date of the follow-up assessment (3-5 weeks after the patient has taken the final dose of IMP).

Adverse event reporting additional description:

Only adverse reactions (ARs) and serious adverse events (SAEs) were collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Control

Reporting group description:

Non intervention arm

Reporting group title	Rosuvastatin

Reporting group description:

Oral rosuvastatin 10 milligram (mg) dose, once daily, for the duration of a treatment course of IV tobramycin (usually 14 days)

Serious adverse events	Control	Rosuvastatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)	1 / 21 (4.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood test			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Control	Rosuvastatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	5 / 21 (23.81%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Blood cholesterol decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Blood triglycerides decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Blood triglycerides increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Paraesthesia oral			
subjects affected / exposed	0 / 27 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 21 (4.76%) 1	
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 1 / 21 (4.76%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2014	Protocol was updated from version 1.0 to 2.0. Changes were as follows: • Updated inclusion/exclusion criteria. • Changes in randomisation process/contact details and addition of backup randomisation. • The addition of 'Assessment of changes in sputum microbiome'. • Change in the minimum volume of blood collection. • Addition of Sputum sampling. • Simplification on severity/grading of AEs (Section 10.6). • Typographical errors and clarifications were also made throughout.
29 May 2015	Protocol was amended from v2.0 to v3.0 on 03/02/2015. Change was a non-substantial amendment. Protocol was amended from v3.0 to v4.0 on 29/05/2015. Changes were as follows: • The participant approach process has been updated in the Protocol. Sites may now approach participants as soon as they present in the clinic, even if they have had the study information for <24hrs. • Addition of Simepravir to exclusion criteria 5. • Changes to recruitment process for main and substudy.
01 July 2015	Protocol was updated from version 4.0 to 5.0. Changes were as follows: • Update to allow flexibility in terms of when participants can be randomised in the trial so that the research pathway can follow the participant's clinical pathway. • Exclusion criteria 9 (proposing to use safety test result from the past 12 weeks). • Adding Simepravir to 'Medications Not Permitted'.
28 April 2016	Protocol was updated from version 6.0 to 7.0. Changes were as follows: • Removal of Itraconozole from the medications in exclusion criteria • Removal of Indian ancestry from the exclusion criteria • Addition of 'Participants with current elevation in creatine kinase exceeding 2x the upper limit of normal at baseline, or in the past 12 weeks' to exclusion criteria.
07 January 2017	Protocol was updated from version 5.0 to 6.0. Changes were as follows: • Insertion of Schwartz formula.
06 February 2017	Protocol was updated from version 7.0 to 8.0.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported